EUR Research Information Portal

European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1

Published in:
Intensive Care Medicine

Publication status and date:
Published: 01/06/2024

DOI (link to publisher):
10.1007/s00134-024-07369-9

Document Version
Publisher's PDF, also known as Version of record

Document License/Available under:
Article 25fa Dutch Copyright Act

Citation for the published version (APA):
Arabi, Y. M., Belley-Cote, E., Carsetti, A., De Backer, D., Donadello, K., Juffermans, N. P., Hammond, N., Laake, J. H., Liu, D., Maitland, K., Messina, A., Møller, M. H., Poole, D., & European Society of Intensive Care Medicine (2024). European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids. *Intensive Care Medicine*, *50*(6), 813-831. https://doi.org/10.1007/s00134-024-07369-9

Link to publication on the EUR Research Information Portal

Terms and Conditions of Use
Except as permitted by the applicable copyright law, you may not reproduce or make this material available to any third party without the prior written permission from the copyright holder(s). Copyright law allows the following uses of this material without prior permission:

- you may download, save and print a copy of this material for your personal use only;
- you may share the EUR portal link to this material.

In case the material is published with an open access license (e.g. a Creative Commons (CC) license), other uses may be allowed. Please check the terms and conditions of the specific license.

Take-down policy
If you believe that this material infringes your copyright and/or any other intellectual property rights, you may request its removal by contacting us at the following email address: openaccess.library@eur.nl. Please provide us with all the relevant information, including the reasons why you believe any of your rights have been infringed. In case of a legitimate complaint, we will make the material inaccessible and/or remove it from the website.

Erasmus University Rotterdam
Making Minds Matter

SHOUT
SHARE
IT

Intensive Care Med (2024) 50:813–831
https://doi.org/10.1007/s00134-024-07369-9

GUIDELINES

European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids

Yaseen M. Arabi[1*], Emilie Belley-Cote[2], Andrea Carsetti[3], Daniel De Backer[4], Katia Donadello[5,6], Nicole P. Juffermans[7], Naomi Hammond[8,9], Jon Henrik Laake[10], Dawei Liu[11], Kathryn Maitland[12], Antonio Messina[13,14], Morten Hylander Møller[15,16], Daniele Poole[17], Rob Mac Sweeney[18], Jean-Louis Vincent[19], Fernando G. Zampieri[20] and Fayez AlShamsi[21] on behalf of European Society of Intensive Care Medicine

© 2024 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

Purpose: This is the first of three parts of the clinical practice guideline from the European Society of Intensive Care Medicine (ESICM) on resuscitation fluids in adult critically ill patients. This part addresses fluid choice and the other two will separately address fluid amount and fluid removal.

Methods: This guideline was formulated by an international panel of clinical experts and methodologists. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was applied to evaluate the certainty of evidence and to move from evidence to decision.

Results: For volume expansion, the guideline provides conditional recommendations for using crystalloids rather than albumin in critically ill patients in general (moderate certainty of evidence), in patients with sepsis (moderate certainty of evidence), in patients with acute respiratory failure (very low certainty of evidence) and in patients in the perioperative period and patients at risk for bleeding (very low certainty of evidence). There is a conditional recommendation for using isotonic saline rather than albumin in patients with traumatic brain injury (very low certainty of evidence). There is a conditional recommendation for using albumin rather than crystalloids in patients with cirrhosis (very low certainty of evidence). The guideline provides conditional recommendations for using balanced crystalloids rather than isotonic saline in critically ill patients in general (low certainty of evidence), in patients with sepsis (low certainty of evidence) and in patients with kidney injury (very low certainty of evidence). There is a conditional recommendation for using isotonic saline rather than balanced crystalloids in patients with traumatic brain injury (very low certainty of evidence). There is a conditional recommendation for using isotonic crystalloids rather than small-volume hypertonic crystalloids in critically ill patients in general (very low certainty of evidence).

*Correspondence: arabi@mngha.med.sa
[1] Intensive Care Department, King Abdulaziz Medical City, Ministry of National Guard—Health Affairs, King Abdullah International Medical Research Center, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
Full author information is available at the end of the article

Springer

Conclusions: This guideline provides eleven recommendations to inform clinicians on resuscitation fluid choice in critically ill patients.

Keywords: Albumin, Crystalloid solutions, Colloid solutions, Practice guidelines, Critical care, Fluid therapy

Introduction

Administration of resuscitation fluids is common in the management of critically ill patients [1]. The European Society of Intensive Care Medicine (ESICM) convened a group of content and method experts to issue a clinical practice guideline (CPG) on fluid management in adult critically ill patients. This CPG was divided into three parts: the choice of resuscitation fluids (part 1), the amount of resuscitation fluids (part 2), and fluid removal in the de-escalation phase (part 3). The full list of contributors is presented in the online electronic supplementary material (ESM). In this manuscript, the guideline on the choice of resuscitation fluid will be presented.

Resuscitation fluids are categorized into crystalloids, including isotonic saline and balanced crystalloids, and colloids, with albumin as the reference colloid solution [2]. In clinical practice, the choice of resuscitation fluids varies according to fluid availability, understanding of the physiologic characteristics of different fluids, clinician preferences, practice setting and region [3].

The aim of this CPG from ESICM was to provide evidence-based guidance regarding the choice of resuscitation fluid in adult critically ill patients supported by a critical analysis of the literature.

Methods

Guideline scope and target audience

The scope of this guideline was to provide evidence-based guidance regarding the choice of early resuscitation fluid in adult critically ill patients due to various etiologies. The target audience for this guideline is front-line clinicians (medical and nursing), allied healthcare workers and policymakers in both high- and low-to-middle-income contexts.

Panel selection and organization

Panel members were appointed with consideration of diversity and inclusivity as previously described [4]. The panel consisted of two ESICM Guidelines Co-chairs, one Clinical Chair, two Methods Co-Chairs from ESICM and Guidelines in Intensive Care, Development and Evaluation (GUIDE) group, the Chairperson of the Methodology Group of ESICM, and 11 experts, including clinicians specialized in critical care, anesthesia, infectious diseases and emergency medicine as well as critical care nursing.

Take-home message

For volume expansion, the guideline provides conditional recommendations for using crystalloids rather than albumin in critically ill patients in general, in patients with sepsis, in patients with acute respiratory failure and in patients in the perioperative period and patients at risk for bleeding. There are conditional recommendations for using isotonic saline rather than albumin in patients with traumatic brain injury and for using albumin rather than crystalloids in patients with cirrhosis. The guideline provides conditional recommendations for using balanced crystalloids rather than isotonic saline in critically ill patients in general, in patients with sepsis and in patients with kidney injury. There are conditional recommendations for using isotonic saline rather than balanced crystalloids in patients with traumatic brain injury and for using isotonic crystalloids rather than small-volume hypertonic crystalloids in critically ill patients in general.

The roles of the panel members are outlined in the online electronic supplementary material (ESM).

Conflict of interest management

We applied the principles of management of conflict of interest (COI) as previously described [5]. Panelists were requested to declare any intellectual or financial COI that may influence their participation in the guideline by completing a special form per the ESICM procedures. A summary of individual declarations is provided at the end of the document under the COI section. Panelists received no financial incentives for their participation. In addition, no funding or input from the industry was incorporated into the guideline.

Development of questions and outcomes selection

This guideline addressed the use of commonly used resuscitation fluids in adult critically ill patients: crystalloids (isotonic saline and balanced crystalloids) and albumin. One question addressed small-volume hypertonic or isotonic crystalloids. This guideline did not address other colloids, such as hydroxyethyl starch (HES) or gelatin. In addition, these guidelines did not address fluid choice for managing burns, the use of hypertonic solutions for the management of increased intracranial pressure or the use of albumin solutions to increase serum albumin levels [6, 7].

At the beginning of the process of the guideline development, the panel proposed several questions according to the Population, Intervention, Comparison,

and Outcomes (PICO) format. After deliberations, the panel prioritized eleven questions, which were approved by the guideline leadership. These questions included the following areas: (A) albumin vs. crystalloids (six questions; in critically ill patients in general, patients with sepsis, patients with acute respiratory failure, patients with traumatic brain injury (TBI), patients in the perioperative period and in patients with bleeding or at risk for bleeding and patients with cirrhosis); (B) balanced crystalloids vs. isotonic saline (four questions; in critically ill patients in general, patients with sepsis, patients with TBI, and patients with acute kidney injury); (C) one question for small-volume hypertonic vs. isotonic crystalloids.

Panelists selected and prioritized outcomes for each PICO on a scale from 1 to 9 (ranging from unimportant to critical) [8]. The following outcomes judged as being critical were included: short-term mortality, need for renal replacement therapy, ventilator-free days/duration of mechanical ventilation, intensive care unit (ICU)-free days/ICU length of stay, hospital-free days/hospital length of stay, quality of life and functional outcomes. For the questions regarding patients with TBI, the additional critical outcome of the extended Glasgow Outcome Scale (GOSE) was used.

Literature search

Methodologists searched for relevant systematic reviews and meta-analyses and updated them when needed. When neither was available, we searched for randomized controlled trials in MEDLINE & EMBASE from inception to April 2022, and any relevant trials published subsequently were also included. We used and updated the search, as relevant, from the reviews by Lewis et al., Tseng et al. and Bai et al. for the questions related to albumin vs. crystalloids [9–11], by Hammond et al., Zampieri et al. and Wan et al. for the questions related to balanced crystalloids vs. isotonic saline [12–14] and by Orbegozo et al. for small-volume hypertonic vs. isotonic crystalloids [15]. Although not included in the grading process, data from observational studies were deliberated in panel meetings, as applicable.

Data analysis

The DerSimonian and Laird random-effects model was used when pooling results of effect sizes across randomized controlled trials (RCTs) [16, 17]. Relative risks (RRs) with corresponding 95% confidence intervals (CIs) were used for binary outcomes, while mean differences (MDs) and 95% CIs were used for continuous outcomes. The I^2 statistic was used for descriptive and not inferential purposes, and heterogeneity was assessed mainly on a clinical basis. All analyses were performed using Review Manager (RevMan) [Version 5.4, The Cochrane Collaboration, 2020] [18]. Updated RevMan data from Lewis et al were used [9]. In addition, published results from Bayesian meta-analysis or individual patient data meta-analysis were also included when evaluating the evidence. The results of systematic reviews were reported according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidance, considering the size of effect and certainty of evidence [19].

Risk of bias and certainty of evidence

The Cochrane Collaboration Risk of Bias (ROB) 1.0 tool was used to assess the risk of bias of individual RCTs. The GRADE methodology was applied to evaluate the certainty of evidence [20]. Accordingly, the certainty of evidence from randomized controlled trials for each critical outcome started with a high rating, but it could be downgraded by one or two points for each of the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [21]. If the evidence was primarily based on study subgroups, the validity of the findings was deliberated during the panel discussions. The certainty of evidence for each recommendation was determined considering the totality of evidence across all outcomes including the critical outcome with the lowest certainty [22]. In addition and in line with the GRADE methodology, the panel also considered the relative importance of each outcome so that the whole body of evidence is not downgraded based on the lower confidence in estimates of the effects of a less critical outcome. For each PICO, we reported the level of certainty for each outcome, the level of certainty for the whole body of evidence and the domains that were involved in downgrading in the corresponding Summary of Evidence section, and provided a more detailed description in the Evidence Profile tables in the ESM. The GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University and Evidence Prime, 2022. Available from www.gradepro.org) was used to create evidence profiles for each PICO.

Recommendation formulation

The panel met online monthly and used the Evidence-to-Decision (EtD) Framework to formulate recommendations [23]. As described in the GRADE methodology, the panel considered the following factors: magnitude of effect, certainty of evidence, patient values and preferences, resources and cost, equity, acceptability, and feasibility when deciding the direction and strength of recommendations. A strong recommendation in favor of an intervention (reported as "we recommend") implies

that the desirable benefit of the intervention outweighs undesirable effects, that most patients and clinicians would choose the recommendation, and that it can be adopted as a policy. On the other hand, a conditional recommendation in favor of an intervention (reported as "we suggest") implies that the desirable benefit of the intervention outweighs the undesirable effects but with a low confidence. It implies that a majority, but not all, individuals will likely be best served by the recommended course of action [23], and that most patients and clinicians, but not all, would accept the suggested action from a conditional recommendation, and for policymakers, it would not be appropriate to be adopted as a policy. To provide practical guidance to critical practitioners, we presented the recommendations in favor of a particular approach rather than against an alternative [24]. The panel used consensus to formulate recommendations and all members approved the final recommendations. A family member of a critically ill patient reviewed the recommendations, provided feedback and supported all eleven recommendations. For each PICO, the panel identified unresolved questions and research gaps as relevant.

Results

Albumin vs. crystalloids

Question 1: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients in general?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in adult critically ill patients in general.
Conditional recommendation, moderate certainty of evidence.

Remark

Questions 2, 3, 4, 5 and 6 address the use of albumin vs. crystalloids in adult critically ill patients with sepsis , adult critically ill patients with acute respiratory failure, adult critically ill patients with TBI, adult critically ill patients in the perioperative period and those with bleeding or at risk for bleeding and adult critically ill patients with cirrhosis, respectively.

Background

Albumin has been advocated as a more effective fluid for expanding intravascular volume than crystalloids because it is believed to be more effectively retained within the intravascular space and that it maintains the intravascular oncotic pressure [3]. Based on early physiologic considerations, albumin has been considered volume-sparing, expanding intravascular volume at a ratio of 1:3 compared to crystalloids [3]. Albumin has been associated with less interstitial edema compared to crystalloids [3]. However, the importance of oncotic pressure in maintaining circulating volume has been challenged by physiologists, pointing toward a possible regulating role for filtration in micro-vessels [25]. Potentially in line with this view, recent RCTs have failed to demonstrate any advantage of albumin over crystalloids on patient-centered outcomes. The volume-sparing effect of albumin is probably less pronounced and shorter-lasting than initially thought. In the SAFE (the Saline versus Albumin Fluid Evaluation) trial, a double-blind RCT, the ratios of the albumin volume to the saline volume ranged from 1:1.2 to 1:1.6 [26].

Summary of the evidence

A pooled analysis of RCTs showed that albumin compared with crystalloids in critically ill patients resulted in little to no difference in mortality [16 trials, $n = 11{,}896$, RR 0.98, 95% CI 0.93, 1.04, I^2 0%, high certainty of evidence, Fig. 1 and ESM]. Albumin versus crystalloids might have not resulted in a difference in renal replacement therapy (5 trials, $n = 3508$, RR 1.04, CI 0.88, 1.24, I^2 29%, low certainty of evidence). In critically ill patients in general, albumin versus crystalloids did not result in a difference in the duration of mechanical ventilation (high certainty of evidence), might have not affected ICU length of stay (low certainty of evidence), and might have had little to no effect on hospital length of stay but the evidence was very uncertain. There was no data on albumin versus crystalloids' impact on quality of life (ESM). The balance of effects did not favor albumin over crystalloids for volume expansion in critically ill patients, and the certainty of the whole body of evidence across all outcomes was moderate (downgraded for imprecision).

The panel considered additional issues when formulating recommendations for using albumin versus crystalloid solutions (EtD framework, ESM). First, the cost of albumin is higher than that of crystalloids [27, 28]. In an international survey, albumin was approximately 27 times more costly than an equivalent dose of isotonic saline, with 1 mL of 4% albumin being considered an equivalent dose to 1.4 mL of saline based on data from the SAFE trial [26, 28]. Data on cost-effectiveness are limited, but some studies have demonstrated that albumin use might be cost-effective in selected populations [29, 30]. Other studies have shown that albumin is not cost-effective, especially in low-resource settings [31, 32]. Second, the widespread use of albumin may negatively impact the equitable use of healthcare resources. Third, albumin is not available in many resource-limited settings. Fourth, albumin is procured from human blood and, as such, is a limited resource. Fifth, regarding patient values and preferences, the panel felt that most patients would likely find albumin administration acceptable. However, some patients who avoid blood products may

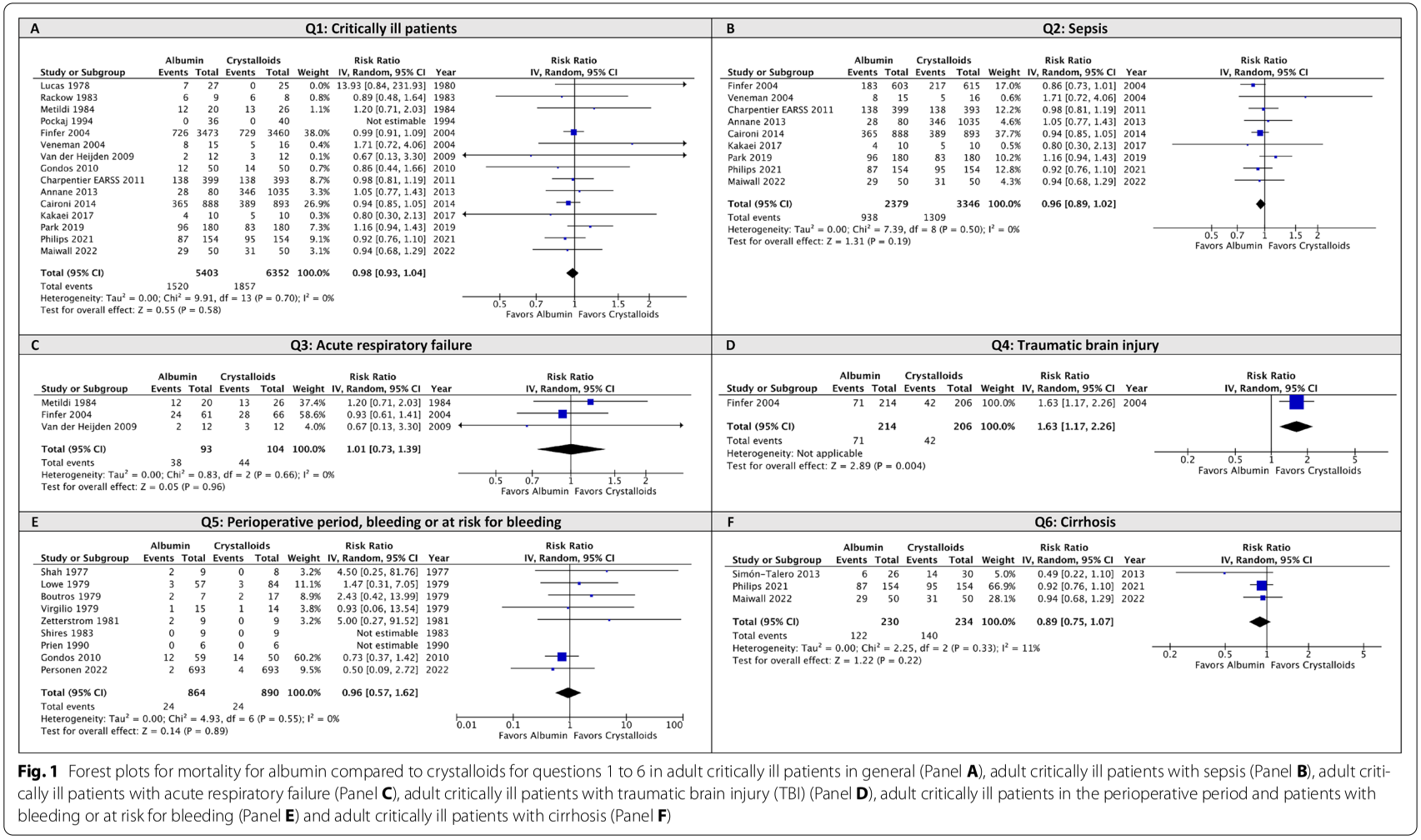
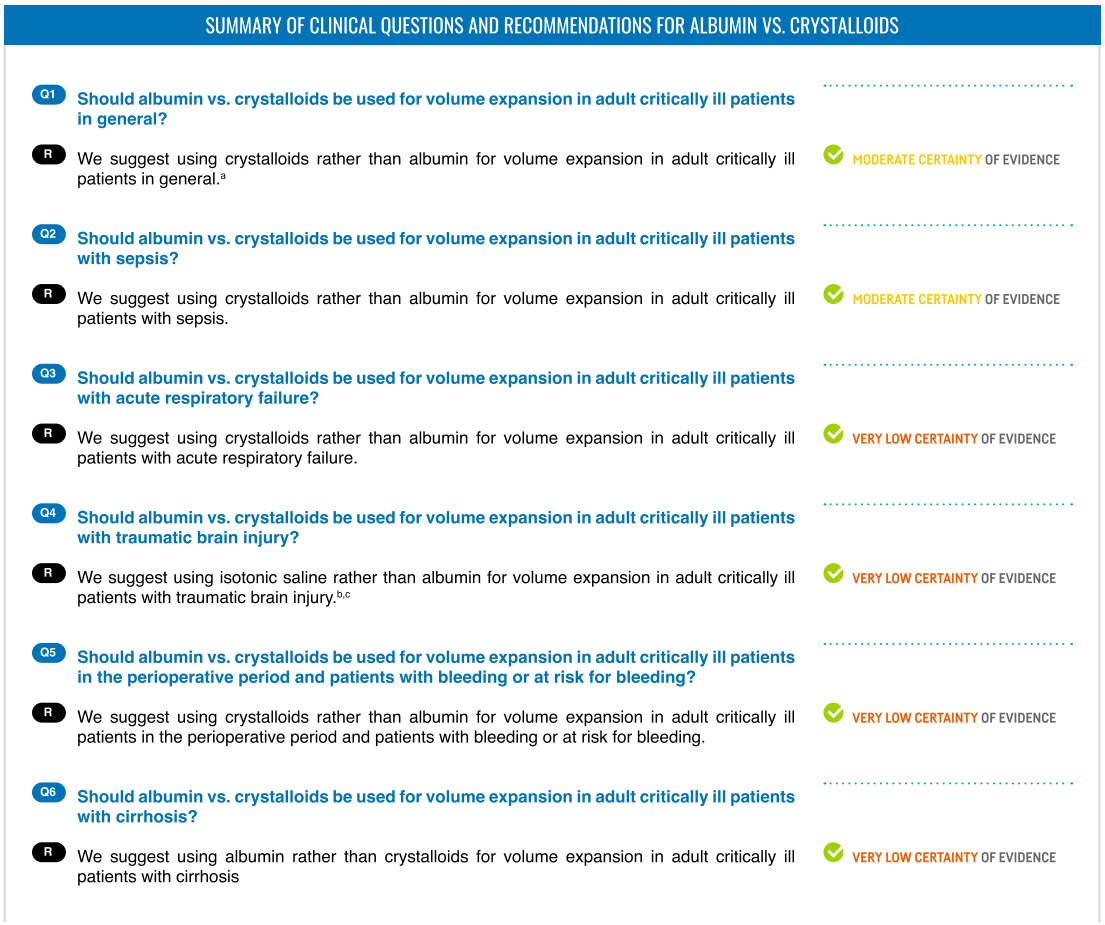

A
Q1: Critically ill patients
Albumin
Crystalloids
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Lucas 1978 7 27 0 25 0.0% 13.93 [0.84, 231.93] 1980
Rackow 1983 6 9 6 8 0.8% 0.89 [0.48, 1.64] 1983
Metildi 1984 12 20 13 26 1.1% 1.20 [0.71, 2.03] 1984
Pockaj 1994 0 36 0 40 Not estimable 1994
Finfer 2004 726 3473 729 3460 38.0% 0.99 [0.91, 1.09] 2004
Veneman 2004 8 15 5 16 0.4% 1.71 [0.72, 4.06] 2004
Van der Heijden 2009 2 12 3 12 0.1% 0.67 [0.13, 3.30] 2009
Gondos 2010 12 50 14 50 0.7% 0.86 [0.44, 1.66] 2010
Charpentier EARSS 2011 138 399 138 393 8.7% 0.98 [0.81, 1.19] 2011
Annane 2013 28 80 346 1035 3.3% 1.05 [0.77, 1.43] 2013
Caironi 2014 365 888 389 893 26.9% 0.94 [0.85, 1.05] 2014
Kakaei 2017 4 10 5 10 0.3% 0.80 [0.30, 2.13] 2017
Park 2019 96 180 83 180 7.3% 1.16 [0.94, 1.43] 2019
Philips 2021 87 154 95 154 9.1% 0.92 [0.76, 1.10] 2021
Maiwall 2022 29 50 31 50 3.1% 0.94 [0.68, 1.29] 2022
Total (95% CI) 5403 6352 100.0% 0.98 [0.93, 1.04]
Total events 1520 1857
Heterogeneity: Tau² = 0.00; Chi² = 9.91, df = 13 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
0.5 0.7 1 1.5 2
Favors Albumin Favors Crystalloids
B
Q2: Sepsis
Albumin
Crystalloids
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Finfer 2004 183 603 217 615 17.0% 0.86 [0.73, 1.01] 2004
Veneman 2004 8 15 5 16 0.6% 1.71 [0.72, 4.06] 2004
Charpentier EARSS 2011 138 399 138 393 12.2% 0.98 [0.81, 1.19] 2011
Annane 2013 28 80 346 1035 4.6% 1.05 [0.77, 1.43] 2013
Caironi 2014 365 888 389 893 37.7% 0.94 [0.85, 1.05] 2014
Kakaei 2017 4 10 5 10 0.5% 0.80 [0.30, 2.13] 2017
Park 2019 96 180 83 180 10.2% 1.16 [0.94, 1.43] 2019
Philips 2021 87 154 95 154 12.8% 0.92 [0.76, 1.10] 2021
Maiwall 2022 29 50 31 50 4.3% 0.94 [0.68, 1.29] 2022
Total (95% CI) 2379 3346 100.0% 0.96 [0.89, 1.02]
Total events 938 1309
Heterogeneity: Tau² = 0.00; Chi² = 7.39, df = 8 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)
0.5 0.7 1 1.5 2
Favors Albumin Favors Crystalloids
C
Q3: Acute respiratory failure
Albumin
Crystalloids
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Metildi 1984 12 20 13 26 37.4% 1.20 [0.71, 2.03] 1984
Finfer 2004 24 61 28 66 58.6% 0.93 [0.61, 1.41] 2004
Van der Heijden 2009 2 12 3 12 4.0% 0.67 [0.13, 3.30] 2009
Total (95% CI) 93 104 100.0% 1.01 [0.73, 1.39]
Total events 38 44
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
0.5 0.7 1 1.5 2
Favors Albumin Favors Crystalloids
D
Q4: Traumatic brain injury
Albumin
Crystalloids
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Finfer 2004 71 214 42 206 100.0% 1.63 [1.17, 2.26] 2004
Total (95% CI) 214 206 100.0% 1.63 [1.17, 2.26]
Total events 71 42
Heterogeneity: Not applicable
Test for overall effect: Z = 2.89 (P = 0.004)
0.2 0.5 1 2 5
Favors Albumin Favors Crystalloids
E
Q5: Perioperative period, bleeding or at risk for bleeding
Albumin
Crystalloids
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Shah 1977 2 9 0 8 3.2% 4.50 [0.25, 81.76] 1977
Lowe 1979 3 57 3 84 11.1% 1.47 [0.31, 7.05] 1979
Boutros 1979 2 7 2 17 8.9% 2.43 [0.42, 13.99] 1979
Virgilio 1979 1 15 1 14 3.8% 0.93 [0.06, 13.54] 1979
Zetterstrom 1981 2 9 0 9 3.2% 5.00 [0.27, 91.52] 1981
Shires 1983 0 9 0 9 Not estimable 1983
Prien 1990 0 6 0 6 Not estimable 1990
Gondos 2010 12 59 14 50 60.2% 0.73 [0.37, 1.42] 2010
Personen 2022 2 693 4 693 9.5% 0.50 [0.09, 2.72] 2022
Total (95% CI) 864 890 100.0% 0.96 [0.57, 1.62]
Total events 24 24
Heterogeneity: Tau² = 0.00; Chi² = 4.93, df = 6 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
0.01 0.1 1 10 100
Favors Albumin Favors Crystalloids
F
Q6: Cirrhosis
Albumin
Crystalloids
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Simón-Talero 2013 6 26 14 30 5.0% 0.49 [0.22, 1.10] 2013
Philips 2021 87 154 95 154 66.9% 0.92 [0.76, 1.10] 2021
Maiwall 2022 29 50 31 50 28.1% 0.94 [0.68, 1.29] 2022
Total (95% CI) 230 234 100.0% 0.89 [0.75, 1.07]
Total events 122 140
Heterogeneity: Tau² = 0.00; Chi² = 2.25, df = 2 (P = 0.33); I² = 11%
Test for overall effect: Z = 1.22 (P = 0.22)
0.2 0.5 1 2 5
Favors Albumin Favors Crystalloids

Fig. 1 Forest plots for mortality for albumin compared to crystalloids for questions 1 to 6 in adult critically ill patients in general (Panel **A**), adult critically ill patients with sepsis (Panel **B**), adult critically ill patients with acute respiratory failure (Panel **C**), adult critically ill patients with traumatic brain injury (TBI) (Panel **D**), adult critically ill patients in the perioperative period and patients with bleeding or at risk for bleeding (Panel **E**) and adult critically ill patients with cirrhosis (Panel **F**)

Table 1 Summary of clinical questions and recommendations for albumin vs. crystalloids


SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR ALBUMIN VS. CRYSTALLOIDS
Q1 Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients in general?
R We suggest using crystalloids rather than albumin for volume expansion in adult critically ill patients in general.[a]
MODERATE CERTAINTY OF EVIDENCE
Q2 Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with sepsis?
R We suggest using crystalloids rather than albumin for volume expansion in adult critically ill patients with sepsis.
MODERATE CERTAINTY OF EVIDENCE
Q3 Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with acute respiratory failure?
R We suggest using crystalloids rather than albumin for volume expansion in adult critically ill patients with acute respiratory failure.
VERY LOW CERTAINTY OF EVIDENCE
Q4 Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with traumatic brain injury?
R We suggest using isotonic saline rather than albumin for volume expansion in adult critically ill patients with traumatic brain injury.[b,c]
VERY LOW CERTAINTY OF EVIDENCE
Q5 Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients in the perioperative period and patients with bleeding or at risk for bleeding?
R We suggest using crystalloids rather than albumin for volume expansion in adult critically ill patients in the perioperative period and patients with bleeding or at risk for bleeding.
VERY LOW CERTAINTY OF EVIDENCE
Q6 Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with cirrhosis?
R We suggest using albumin rather than crystalloids for volume expansion in adult critically ill patients with cirrhosis
VERY LOW CERTAINTY OF EVIDENCE
CERTAINTY OF EVIDENCE:
NO EVIDENCE / VERY LOW / LOW / MODERATE / HIGH
Q QUESTION
R RECOMMENDATION
REMARK
NO RECOMMENDATION
CONDITIONAL RECOMMENDATION
STRONG RECOMMENDATION
CONDITIONAL RECOMMENDATION AGAINST
STRONG RECOMMENDATION AGAINST

[a] Specific recommendations are made for adult critically ill patients with sepsis (Question 2), acute respiratory failure (Question 3), traumatic brain injury (Question 4), patients in the perioperative period and patients with bleeding or at risk for bleeding (Question 5) or cirrhosis (Question 6)

[b] Existing data compares isotonic saline, but not balanced crystalloids, to albumin

[c] A specific recommendation is made for the use of balanced crystalloids vs. isotonic saline in adult critically ill patients with traumatic brain injury (Question 9)

not accept the use of albumin [3]. Rare allergic reactions may also cause some to prefer to avoid albumin [33, 34]. With all these considerations, the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in critically ill patients in general (Table 1).

Unresolved questions and research gaps

Studies are needed for albumin solutions in different concentrations, and for the interaction of albumin effect with the volume of crystalloids administered contemporaneously.

Question 2: Should Albumin vs. crystalloids be used for volume expansion in adult critically ill patients with sepsis?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in adult critically ill patients with sepsis.
Conditional recommendation, moderate certainty of evidence.

Background

Patients with sepsis have decreased vascular tone, increased venous capacitance, and capillary leak, and may respond to fluid resuscitation [35]. However,

resuscitation fluids will eventually distribute into the interstitial and intracellular spaces, especially if endothelial integrity is impaired, leading to a gradual loss of effect of fluid administration [35, 36]. In addition, the resulting interstitial edema has been associated with organ dysfunction in sepsis. Albumin may have potential advantages over crystalloids in patients with sepsis and is believed to afford greater plasma-expanding capacity than crystalloids by maintaining the oncotic pressure in the intravascular compartment [3]. In addition, albumin has several pleiotropic properties not related to fluid volume [37–40].

Summary of the evidence

For patients with sepsis, the pooled analysis demonstrated that albumin versus crystalloids in patients with sepsis did not result in a difference in mortality (9 trials, $n = 5725$, RR 0.96, 95% CI 0.89–1.02, I^2 0%, high certainty of evidence, Fig. 1 and ESM). In the CRISTAL (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill) trial, patients were randomized to receive colloids (gelatines, dextrans, hydroxyethyl starches, or 4% or 20% of albumin) or crystalloids [41]. Because randomization was not stratified according to the type of colloid, we conducted a sensitivity analysis excluding the patients from this trial, and the results did not change. Albumin versus crystalloids probably did not result in a difference in renal replacement therapy (5 trials, $n = 3508$, RR 1.04, CI 0.88, 1.24, I^2 29%, moderate certainty of evidence). In patients with sepsis, albumin versus crystalloids probably did not affect ICU length of stay (moderate certainty of evidence), might not have resulted in a difference in ventilator-free days (low certainty of evidence), and might have had little to no effect on mechanical ventilation duration and hospital length of stay but the evidence was very uncertain. The balance of effects did not favor albumin over crystalloids for volume expansion in patients with sepsis. The certainty of the whole body of evidence was moderate (downgraded for imprecision).

Considering the increased cost and limited availability of albumin and the additional considerations listed earlier (under question 1), the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in patients with sepsis (Table 1).

Does albumin have a role in selected groups of patients with sepsis? The panel discussed thoroughly the potential role of albumin in the following selected groups: patients with hypo-albuminemia, patients who received large volumes of crystalloids and patients with septic shock. Trials in these specific patient groups have been limited; hence, the role of albumin in these groups remains an area of uncertainty. A sub-study from the SAFE trial evaluated whether outcomes of resuscitation with albumin or isotonic saline in critically ill patients depend on patients' baseline serum albumin concentration [42]. In this sub-study, which included 6045 patients, 25% of whom had sepsis on admission, the odds ratios for death for albumin compared with saline for patients with a baseline serum albumin concentration of 25 g/l or less and more than 25 g/l were 0.87 and 1.09, respectively (ratio of odds ratios 0.80, 95% CI 0.63–1.02, P value = 0.08 for heterogeneity) [42]. Given the limited existing data, there were different views among the panelists about using albumin for volume expansion for patients with hypo-albuminemia, patients who received large volumes of crystalloids and patients with septic shock. Therefore, no recommendations for or against using albumin in these groups were issued.

Unresolved questions and research gaps

The choice of fluid in different phases of sepsis therapy (resuscitation, optimization, stabilization, and evacuation) is still largely unclear and requires further study [43]. The role of concentrated albumin as a resuscitation fluid in patients with sepsis is unclear. Further studies need to evaluate whether there are specific groups of patients with sepsis in which albumin improves outcomes. Fluid choice in resource-limited settings needs to be evaluated. Cost-effective analyses of using albumin in patients with sepsis are required across different settings and patient populations, including those with hypoalbuminemia.

Question 3: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with acute respiratory failure?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in adult critically ill patients with acute respiratory failure.
Conditional recommendation, very low certainty of evidence.

Background

Acute respiratory distress syndrome (ARDS) is a major cause of acute respiratory failure [44, 45]. One of the hallmark features of ARDS is the increased alveolar-capillary permeability resulting in the accumulation of fluids into the alveolar space [46]. Fluid filtration across the alveolar-capillary barrier has traditionally been viewed according to the classic Starling model

[47]. In this model, fluid filtration is mainly determined by the hydrostatic gradient and oncotic gradient, and the interstitial space is considered to have a low protein concentration. It is now recognized that the interstitial space has a high protein concentration, limiting the oncotic gradient and reducing fluid return to the plasma compartment and that much of the residual fluid in the interstitial space is removed through the lymphatic system [47].

The optimal fluid for patients with acute respiratory failure (including ARDS) is a fluid that corrects hemodynamic instability and improves tissue perfusion without inducing pulmonary interstitial edema and compromising pulmonary function. There are data suggesting that albumin used concurrently with furosemide improves oxygenation in patients with ARDS compared to crystalloids [48].

Summary of the evidence

The literature search identified 3 RCTs, with a total of 197 participants randomized to receive either albumin or crystalloids in acute respiratory failure (ARF). This included data from a subgroup in the SAFE trial [26], comprised of only 123 of 6997 randomized patients (1.8%, not stratified by ARF) and two other small studies (46 and 24 patients randomized) [49, 50]. The pooled analysis demonstrated that albumin, compared to crystalloids, in patients with acute respiratory failure had no effect on mortality, but the evidence was very uncertain (RR 1.01, 95% CI 0.73–1.39, I^2 0%, very low certainty of evidence, Fig. 1 and ESM). No other outcomes were reported for this population (ESM). The balance of benefits and harms of either strategy did not favor albumin or crystalloids, and the certainty of the whole body of evidence was very low (downgraded for risk of bias and imprecision, ESM).

Considering the factors discussed earlier, including the cost, equity, availability, and patient preferences, the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in patients with ARF (Table 1).

Unresolved questions and research gaps

There are no published clinical trials that have evaluated the effect of albumin or other types of fluids on patient-centered outcomes in ARDS. There is also a need to investigate the cost-effectiveness of albumin and its effects on long-term outcomes in patients with ARDS.

Question 4: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with traumatic brain injury (TBI)?

Recommendation

We **suggest** using isotonic saline rather than albumin for volume expansion in adult critically ill patients with TBI.
Conditional recommendation, very low certainty of evidence.

Remark

Existing RCT data compares isotonic saline, but not balanced crystalloids, to albumin.

Question 9 addresses the use of balanced crystalloids vs isotonic saline in adult critically ill patients with TBI.

Background

Current management of severe TBI is centered on maintaining adequate cerebral perfusion pressure, necessitating treatment with intravenous fluids and vasopressors [51]. Concerns about the safety of 4% albumin were raised based on the subgroup analysis from the SAFE trial [26].

Summary of the evidence

In the literature review of RCTs comparing albumin with crystalloids in patients with TBI, we identified only the subgroup analysis from the SAFE trial [10, 52]. The analysis demonstrated that using 4% albumin compared to isotonic saline for volume expansion in the subgroup of patients with TBI might have increased mortality at day 28, but the evidence was very uncertain (26.1% vs. 15.7%, RR 1.68, 95% CI 1.16–2.43, P value = 0.005, very low certainty of evidence Fig. 1 and ESM). A long-term follow-up study demonstrated that mortality at two years might have remained higher in the albumin group, but the evidence was very uncertain (420 patients, 33.2% vs. 20.4%, RR 1.63, 95% CI 1.17–2.26, P value = 0.003, very low certainty of evidence, Fig. 1 and ESM) [52]. Patients in the albumin group might less likely have had favorable neurologic outcomes as measured by the GOSE, but the evidence was very uncertain (ESM) [52]. This effect was driven by patients with severe TBI (Glasgow Coma Scale (GCS) score < 9) [52]. A mechanistic study [53] ascribed the excess mortality observed in SAFE-TBI to cerebral edema based on observed higher intracranial pressure in patients in the albumin group compared to the isotonic saline group at the end the first week (19.2 ± 1.07 versus 15.4 ± 1.06 mmHg, P value = 0.01). The balance of benefits and harms favored isotonic saline over albumin, the certainty of the whole body of evidence

across all outcomes was very low (downgraded for the risk of bias and imprecision).

The finding was based on a post hoc subgroup analysis. However, subsequent studies suggested the physiologic plausibility of the finding. The 4% albumin solution used in the study was hypotonic (260 mOsm/L), raising the question of whether excess mortality was due to the hypotonic carrier fluid or to the albumin itself. An animal study designed to answer this question suggested that the albumin solution's hypotonicity might have been a contributing factor [54]. The panel noted that the balance of effects, cost and equity considerations all favored using isotonic saline over albumin. Therefore, the panel made a conditional recommendation for using isotonic saline rather than albumin in TBI patients requiring fluid resuscitation (Table 1).

Unresolved questions and research gaps

No robust data are addressing the safety and efficacy of hyperoncotic (20–25%) human albumin solution in patients with severe TBI [55].

Question 5: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients in the perioperative period and in patients with bleeding or at risk for bleeding?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in critically ill patients in the perioperative period and patients with bleeding or at risk for bleeding.
Conditional recommendation, very low certainty of evidence.

Background

Intravenous infusion of resuscitation fluids not containing coagulation factors impairs coagulation by diluting the plasma [56, 57]. This non-specific dilutional effect on coagulation is determined by the fluid's volume efficacy, which explains why crystalloids, especially when given in large volumes, are more likely than albumin to cause dilutional coagulopathy [56]. In a matched controlled study of trauma patients, low-compared with high-volume crystalloid replacement was associated with reduced coagulopathy, blood transfusion, and mortality, suggesting that the effect is volume-dependent [58]. In addition to the dilutional effect, colloids in general, induce derangements in specific coagulation factors, although these effects are observed the least with albumin compared with other colloids [56].

Summary of the evidence

Based on a recent systematic analysis by Tseng et al., we identified nine trials comparing albumin with crystalloids in adult critically ill patients in the perioperative period and in patients with bleeding or at risk for bleeding [10]. Of these, six trials were performed in patients undergoing major vascular surgery and three were in trauma patients. All studies but one were conducted > 15 years ago. Albumin, compared to crystalloids had no effect on mortality, but the evidence was very uncertain (9 trials, $n = 1754$, RR 0.96, 95% CI 0.57–1.62, I^2 0%, Fig. 1 and ESM). Acute kidney injury was assessed in one study: albumin, compared to crystalloids, had no effect on acute kidney injury, but the evidence was very uncertain. Those receiving albumin had a numerically smaller blood transfusion volume, which was not statistically significant and the evidence was very uncertain (mean difference −224 ml, 95% CI −490, 42, I^2 95%, ESM). The balance of benefits and harms did not favor albumin or crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for risk of bias, indirectness, and imprecision).

Given the balance of effect, in addition to the considerations of albumin versus crystalloids discussed earlier about the cost, equity, availability and patient preferences, the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in patients with or at risk of bleeding (Table 1).

Unresolved questions and research gaps

The available evidence is mostly based on relatively old RCTs, which had limited evaluation of outcomes of interest. More contemporary RCTs are needed to better understand the effect of fluid choice in this population and evaluate the presence of differential effects across patients' subgroups.

Question 6: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with cirrhosis?

Recommendation

We **suggest** using albumin rather than crystalloids for volume expansion in adult critically ill patients with cirrhosis.
Conditional recommendation, very low certainty of evidence.

Background

Advanced cirrhosis is associated with complex hemodynamic changes, characterized by increased splanchnic blood volume and relative central hypovolemia [59].

Infusion of albumin is widely used in cirrhotic patients for intravascular volume expansion. In addition, studies suggest that the administration of albumin may have beneficial effects through its antioxidant and anti-inflammatory effects as well as its binding properties for endogenous and exogenous toxins [59, 60].

In managing patients with cirrhosis, albumin is used for various indications, including decompensated cirrhosis, ascites, encephalopathy, infections, hepatorenal syndrome and hypoalbuminemia [61–63]. Several systematic reviews and CPGs have been published over the years, addressing these indications based on the existing data that varied in settings (mainly hospitalized patients) and comparisons [11, 61–69]. Many of the conducted trials, for example, those evaluating hepatorenal syndrome, included albumin in both study arms, indicating the lack of equipoise in the medical community in some of these indications.

Summary of the evidence

A literature review identified three relevant RCTs based on a recent systematic review by Bai et al., addressing the question of albumin versus crystalloids [11]. One trial was performed on critically ill patients with cirrhosis, while the other two included all hospitalized patients with cirrhosis [70–72]. The studies compared hyper-oncotic albumin in different doses and concentrations. Aggregate data from the three trials on 464 patients showed no statistically significant difference in mortality between albumin and crystalloids, with the point estimate favoring albumin, but the evidence was very uncertain (RR 0.89, 95% CI 0.75–1.07, I^2 11%, very low certainty of evidence, Fig. 1 and ESM). Similar findings were shown when evaluating the need for renal replacement therapy, ICU and hospital lenght of stay (LOS) (all very low certainty of evidence, only one trial included, ESM) [72]. The balance of benefits and harms favored albumin over crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for indirectness and imprecision).

Cost-effectiveness data are limited. One study from Germany, Italy, and Spain demonstrated that albumin was cost-effective in the treatment of decompensated cirrhosis [27]. However, data from low-middle-income countries are lacking. Despite increased costs and reduced equity (EtD framework, ESM), the panel made a conditional recommendation for using albumin rather than crystalloids for volume expansion in critically ill patients with cirrhosis (Table 1).

Unresolved questions and research gaps

Given the limited available data, future work is needed to evaluate the question of albumin vs. crystalloids for volume expansion in adult critically ill patients with cirrhosis. The role of albumin 20% vs 5% in this population for volume expansion requires further study.

Balanced crystalloids vs. isotonic saline

Question 7: Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients in general?

Recommendation
We **suggest** using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients. *Conditional recommendation, low certainty of evidence.*
Remarks
In settings with a limited supply of balanced crystalloids, it is advised to prioritize using balanced crystalloids rather than isotonic saline in patients who require large volumes of resuscitation fluids and those with hyperchloremia or acidosis.
In settings where balanced crystalloids are unavailable, isotonic saline is an acceptable alternative.
Conversely, isotonic saline should be considered in patients with hypochloremia or metabolic alkalosis.
Questions 8, 9 and 10 address the use of balanced crystalloids vs isotonic saline in adult critically ill patients with sepsis , traumatic brain injury , and acute kidney injury, respectively.

Background

Isotonic saline (normal saline, 0.9% saline) is traditionally the most commonly used crystalloid solution worldwide [2, 73]. Because isotonic saline contains sodium and chloride in equal concentrations (each 154 mmol/l), the strong ion difference is zero [3, 74]. As a result, rapid administration of a large volume of isotonic saline can cause hyperchloremic metabolic acidosis. It is recognized now that hyperchloremia may be associated with acute kidney injury [3, 74, 75].

The use of balanced crystalloids has risen over the last few years because of concerns about the adverse effects of isotonic saline [2]. Compared to isotonic saline, balanced crystalloids have lower chloride concentrations by substituting some chloride with an organic anion, such as lactate, acetate, gluconate and malate [3, 74]. Additionally, balanced crystalloids contain cations other than sodium (potassium, calcium and magnesium) [3, 74].

Summary of the evidence

Our literature review, including the recent systematic review and meta-analysis on the topic by Hammond et al. [13] identified 11 studies with a total of 35,884 participants, of which 9 RCTs with 35,644 participants reported the mortality outcome. The pooled estimate demonstrated that balanced crystalloids compared with isotonic saline in adult critically ill patients did not result in a statistically significant difference in mortality (RR 0.93, 95% CI 0.76–1.15, I^2 88.44%). In the same systematic review, the risk ratio (RR) for 90-day mortality with balanced crystalloids versus saline in a pooled analysis from six trials (34,450 participants) with a low risk of bias was 0.96 (95% CI 0.91–1.01, I^2 12.1%). In a Bayesian analysis using vague priors, the posterior probability that balanced crystalloids reduced mortality was 91.69% for all trials and 89.5% for low-risk of bias trials [13]. In an individual patient data meta-analysis (six RCTs, 34653 patients) using a Bayesian regression model, the odds ratio for 90-day mortality with balanced crystalloids versus saline was 0.962 (95% credible interval 0.909–1.019), with an absolute difference −0.4 percentage points [−1.5 to 0.2]) and a posterior probability that balanced solutions reduced mortality of 89.5% [14]. These findings were generally aligned with the findings of a systematic review that included observational studies and RCTs [76]. Collectively, the existing data showed that balanced crystalloids compared with isotonic saline probably resulted in a slight reduction in mortality (moderate certainty of evidence). Balanced crystalloids compared with isotonic saline probably did not result in a difference in renal replacement therapy (low certainty of evidence), might not have changed ventilation-free days (moderate certainty of evidence), did not affect vasopressor-free days or ICU LOS (high certainty of evidence for both outcomes) and probably did not change hospital length of stay (moderate certainty of evidence, ESM). The balance of benefits and harms favored balanced crystalloids over isotonic saline, and the certainty of the whole body of evidence across all outcomes was low (downgraded for risk of bias, imprecision and inconsistency).

Because the balance of benefits and harms favored balanced crystalloids over isotonic saline in critically ill patients, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients (Table 2).

In a 2014 study conducted in 426 ICUs from 27 countries, the average cost for crystalloids overall was less than 1 United States Dollars (USD) per 100 mL, with isotonic saline being the least costly [28]. There was an 11-fold variation in the cost of isotonic saline across countries, ranging from 0.09 to 1.04 USD/100 mL [28]. There was a seven-fold variation in the cost of balanced crystalloids across countries, ranging from 0.14 to 1.04 USD/100 mL [28]. The panel acknowledged the unavailability or limited availability and the higher cost of balanced crystalloids compared to isotonic saline in many settings worldwide, especially in low-income countries [28]. In settings where there is a limited supply of balanced crystalloids, the panel advised to prioritize using balanced crystalloids rather than isotonic saline in patients who require large volumes of resuscitation fluids and in those with hyperchloremia or acidosis. A good practice could be to monitor chloride levels and switch from saline to balanced crystalloids if hyperchloremia develops. In situations where balanced crystalloids are unavailable, isotonic saline was considered an acceptable alternative. Conversely, isotonic saline should be considered in patients with hypochloremia or metabolic alkalosis.

Unresolved questions and research gaps

There is a need to compare the effect of different balanced solutions, e.g., PlasmaLyte, Ringer's lactate or acetate and others on patient-centered outcomes. Trials of guided therapy with balanced crystalloids and isotonic saline are an important next step for critically ill patients. Such trials could, for example, include regular chloride measurements, allowing for prompt intervention in case of hyperchloremia. Additionally, such trials could consider cost variations of fluids and laboratory tests across different settings.

Question 8: Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with sepsis?

Recommendation

We **suggest** using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with sepsis.
Conditional recommendation, low certainty of evidence.

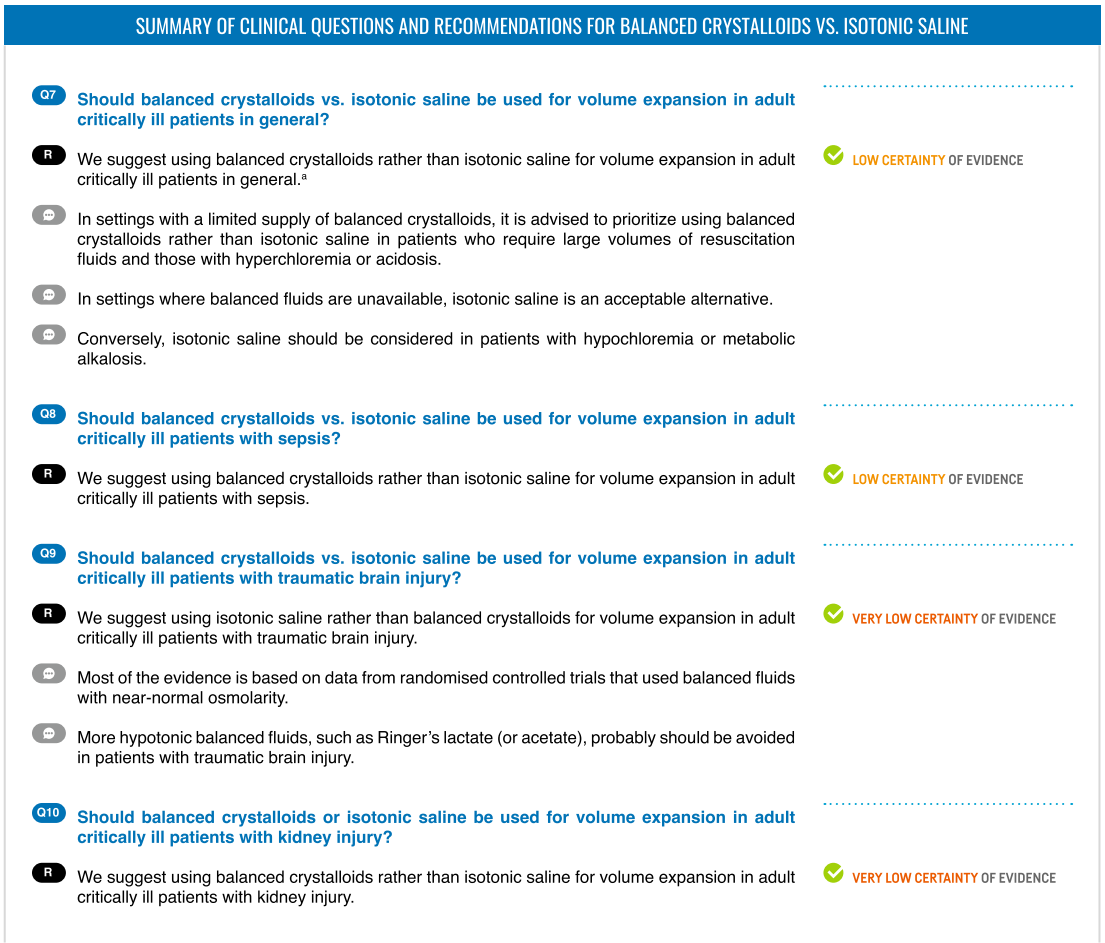
Background

Isotonic saline was globally the most commonly used resuscitation fluid in patients with sepsis until data emerged suggesting that isotonic saline might increase the risk of acute kidney injury due to the high chloride content [77–80]. As a result, balanced crystalloids have gained popularity as the fluid of choice due to their lower chloride content, which mimics human physiologic levels [2].

Summary of the evidence

All recent trials comparing balanced crystalloids to saline evaluated subgroups of patients with sepsis [81–85]. Six

Table 2 Summary of clinical questions and recommendations for balanced crystalloids vs. isotonic saline


SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR BALANCED CRYSTALLOIDS VS. ISOTONIC SALINE
Q7
Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients in general?
R
We suggest using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients in general.[a]
LOW CERTAINTY OF EVIDENCE
In settings with a limited supply of balanced crystalloids, it is advised to prioritize using balanced crystalloids rather than isotonic saline in patients who require large volumes of resuscitation fluids and those with hyperchloremia or acidosis.
In settings where balanced fluids are unavailable, isotonic saline is an acceptable alternative.
Conversely, isotonic saline should be considered in patients with hypochloremia or metabolic alkalosis.
Q8
Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with sepsis?
R
We suggest using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with sepsis.
LOW CERTAINTY OF EVIDENCE
Q9
Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with traumatic brain injury?
R
We suggest using isotonic saline rather than balanced crystalloids for volume expansion in adult critically ill patients with traumatic brain injury.
VERY LOW CERTAINTY OF EVIDENCE
Most of the evidence is based on data from randomised controlled trials that used balanced fluids with near-normal osmolarity.
More hypotonic balanced fluids, such as Ringer's lactate (or acetate), probably should be avoided in patients with traumatic brain injury.
Q10
Should balanced crystalloids or isotonic saline be used for volume expansion in adult critically ill patients with kidney injury?
R
We suggest using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with kidney injury.
VERY LOW CERTAINTY OF EVIDENCE
CERTAINTY OF EVIDENCE:
NO EVIDENCE / VERY LOW / LOW / MODERATE / HIGH
Q QUESTION
R RECOMMENDATION
REMARK
NO RECOMMENDATION
CONDITIONAL RECOMMENDATION
STRONG RECOMMENDATION
CONDITIONAL RECOMMENDATION AGAINST
STRONG RECOMMENDATION AGAINST

[a] Specific recommendations are made for adult critically ill patients with sepsis (Question 8), traumatic brain injury (Question 9), or acute kidney injury (Question 10)

studies contributed to the mortality outcome, including 6914 participants with sepsis [13]. The pooled estimate demonstrated that balanced solutions compared with isotonic saline in adult critically ill patients with sepsis probably did not result in a statistically significant reduction in mortality (RR 0.93, 95% CI 0.85–1.01, I^2 19.26%). In an individual patient data meta-analysis using a Bayesian regression model, the odds ratio for 90-day mortality among patients with sepsis with balanced crystalloids versus isotonic saline was 0.935 (95% credible interval 0.847–1.040) with a posterior probability that balanced solutions reduced mortality of 89.3% [14]. Collectively, the existing data showed that balanced crystalloids compared with isotonic saline probably resulted in a slight reduction in mortality (moderate certainty of evidence). Balanced crystalloids compared with isotonic saline might not have resulted in differences in renal replacement therapy or ventilation-free days (low certainty of evidence for both outcomes) and probably did not affect vasopressor-free days (moderate certainty of evidence) (ESM). The balance of benefits and harms favored balanced crystalloids over isotonic saline, and the certainty of the whole body of evidence across all outcomes was low (downgraded for inconsistency and imprecision).

Based on the available evidence, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in patients with sepsis (Table 2).

Unresolved questions and research gaps

There is a need for trials comparing the effects of different balanced crystalloids on patient-centered outcomes in patients with sepsis.

Question 9: Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with traumatic brain injury (TBI)?

Recommendation

We **suggest** using isotonic saline rather than balanced crystalloids for volume expansion in adult critically ill patients with TBI.
Conditional recommendation, very low certainty of evidence.

Remarks

Most of the evidence is based on data from RCTs that used balanced crystalloids with near-normal osmolarity.

More hypotonic balanced crystalloids, such as Ringer's lactate (or acetate), probably should be avoided in patients with TBI.

Background

Fluid osmolarity is an important consideration in patients with TBI, as low fluid osmolality has been linked to the development of cerebral edema [86]. Isotonic saline is considered the reference solution because it has an osmolarity of 308 mOsmol/L, which is slightly higher than that of the plasma. Balanced crystalloids vary in osmolarity, but they have an osmolarity slightly lower than isotonic saline. Ringer's lactate (or acetate) is slightly hypotonic (osmolarity of Ringer's lactate 273 mOsmol/L) [87] and has been associated with higher mortality among patients with TBI compared to isotonic saline in observational data [88]. However, even other balanced crystalloids that have an osmolality near to the serum osmolality, such as Plasma-Lyte 148 (osmolarity of 294 mOsmol/L), have been linked to increased mortality in recent RCTs (see below).

Summary of the evidence

Based on a recent systematic review, we identified subgroup data from 3 RCTs with a low risk of bias that compared balanced crystalloids with isotonic saline and reported data on mortality for patients with TBI [13, 81, 83, 85, 89]. The balanced crystalloid in two trials was Plasma-Lyte, and in one trial Plasma-Lyte or Ringer's lactate [89]. The pooled analysis ($n = 1896$ participants) demonstrated an increase in mortality with balanced crystalloids compared with isotonic saline (RR 1.25, 95% CI 1.01–1.54; $I^2 = 7\%$). In an individual patient data meta-analysis using a Bayesian regression model, the odds ratio for mortality among patients with TBI with balanced crystalloids compared to isotonic saline was 1.424 (95% credible interval 1.1–1.818) with a high posterior probability (97.5%) that balanced crystalloids increased mortality [14]. Collectively, the existing data showed that balanced crystalloids compared with isotonic saline might have resulted in an increase in mortality (low certainty of evidence). Balanced crystalloids, compared to isotonic saline, had little to no effect on renal replacement therapy but the evidence was very uncertain (very low certainty of evidence) (ESM). There were no reported data on neurologic outcomes. However, a secondary analysis of the SMART trial (Isotonic Solutions and Major Adverse Renal Events trial) demonstrated that balanced crystalloids compared with isotonic saline were associated with worse discharge disposition (death or discharge to another medical facility) in critically injured patients with TBI (adjusted odds ratio [aOR] 1.38, 95% CI 1.02–1.86, P value = 0.04) [89]. The balance of benefits and harms favored isotonic saline over balanced crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for risk of bias, inconsistency, indirectness, and imprecision).

Based on the available evidence, the panel issued a conditional recommendation for using isotonic saline rather than balanced crystalloids for volume expansion in adult critically ill patients with TBI (Table 2). Because most of the evidence is based on data from RCTs that used balanced crystalloids with near-normal osmolarity and because of observational data demonstrating harm of Ringer's lactate in patients with TBI, the panel advised avoiding Ringer's lactate (or acetate), in patients with TBI.

Question 10: Should balanced crystalloids or isotonic saline be used for volume expansion in adult critically ill patients with kidney injury?

Recommendation

We **suggest** using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with kidney injury.
Conditional recommendation, very low certainty of evidence.

Background

Volume expansion in patients with acute kidney injury (AKI) aims to improve tissue perfusion and maintain fluid balance without further compromising kidney function.

Summary of the evidence

Our literature review identified only one small relevant RCT ($n = 38$) comparing balanced crystalloids or isotonic saline in prerenal AKI with pre-established chronic kidney disease (CKD) [90]. Administration of Ringer's lactate or isotonic saline did not result in a significant

difference in short or long-term kidney function, and none of the patients required dialysis [90]. We also identified indirect evidence from RCTs on patients with renal transplantation, including the recently published BEST-Fluids (Better Evidence for Selecting Transplant Fluids) trial [12, 91–93]. In this population, pooled data (8 RCTs, $n=1526$ patients) demonstrated that balanced crystalloids compared to isotonic saline might have reduced renal replacement therapy (RR 0.85, 95% CI 0.73–0.99, I^2 0%, low certainty of evidence) and the need for mechanical ventilation (low certainty of evidence) and probably have reduced delayed graft function (moderate certainty of evidence). There were no significant differences in hospital LOS, but the evidence was very uncertain (ESM). The certainty of the whole body of evidence across all outcomes was very low (downgraded for inconsistency, indirectness, and imprecision).

The costs of balanced crystalloids solutions are modest; their availability varies and is probably limited in resource-poor settings. Taking all the above in consideration, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with acute kidney injury (Table 2).

Unresolved questions and research gaps

There is a need for more data on the choice of balanced crystalloids or isotonic saline for volume expansion in adult critically ill patients with acute kidney injury.

Small-volume hypertonic or isotonic crystalloids

Question 11: Should small-volume hypertonic or isotonic crystalloids be used for volume expansion in adult critically ill patients?

Recommendation

We **suggest** using isotonic crystalloids rather than small-volume hypertonic fluids for volume expansion in adult critically ill patients.
Conditional recommendation, very low certainty of evidence.

Background

Hypertonic saline solution (3%, 5%, 7.5%, 20% or other concentrations) has been investigated in animal models as an alternative to isotonic crystalloids as for the management of hypovolemic, hemorrhagic and septic shock. The hypertonic saline solution provides immediate intravascular volume expansion but with a reduced amount of administered volume [94]. Limited evidence from observational cohorts showed that a positive fluid balance was associated with worse ICU mortality and functional outcomes of TBI patients [95]. It has been shown that hypertonic saline solution, compared to isotonic saline, was associated with improved hemodynamics [96]. Hypertonic saline solution may have favorable anti-inflammatory effects [97]. Because smaller volumes of hypertonic saline are needed to expand intravascular volume, it has an advantage as a resuscitation fluid on the battlefield and in pre-hospital settings [98–100]. However, the high chloride content of hypertonic saline may have adverse effects, including acidosis, coagulopathy, and impaired renal function [101]. Of note, the use of hypertonic saline in patients with traumatic brain injury (TBI) as a bolus in a pre-hospital setting or as a continuous infusion in the ICU has not improved either short-term or long-term outcomes compared to patients who received conventional fluids [100, 102].

Summary of the evidence

Our literature search, including reviewing existing systematic reviews [15, 103–107] identified 17 RCTs comparing hypertonic saline solution to isotonic crystalloids in patients with trauma, hypovolemia, sepsis, and surgery. Pooled analysis suggested that hypertonic saline solution compared to isotonic crystalloids in adult critically ill patients did not reduce mortality (17 trials, $n=2195$, RR 0.99, 95% CI 0.88–1.12, I^2 0%, low certainty of evidence, Fig. 2 and ESM). The analysis also suggested that hypertonic saline solution compared to isotonic crystalloids did not result in a difference in renal replacement therapy, ventilation-free days, ICU length of stay, or functional outcomes (low certainty of evidence for the four outcomes) and the evidence about hospital length of stay was very uncertain (very low certainty of evidence, ESM). The balance of benefits and harms did not favor small-volume hypertonic or isotonic crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for risk of bias, inconsistency, and imprecision).

The balance of effects did not favor either hypertonic saline solution to isotonic crystalloids. However, given the variable availability, the additional cost, and the limited acceptability of hypertonic saline among critical care practitioners, the panel issued a conditional recommendation for using isotonic crystalloids rather than small volume hypertonic fluids for volume expansion (Table 3).

Unresolved questions and research gaps

Further research is required to identify if there are subgroups of adult critically ill patients who may benefit from hypertonic saline for volume expansion [108].

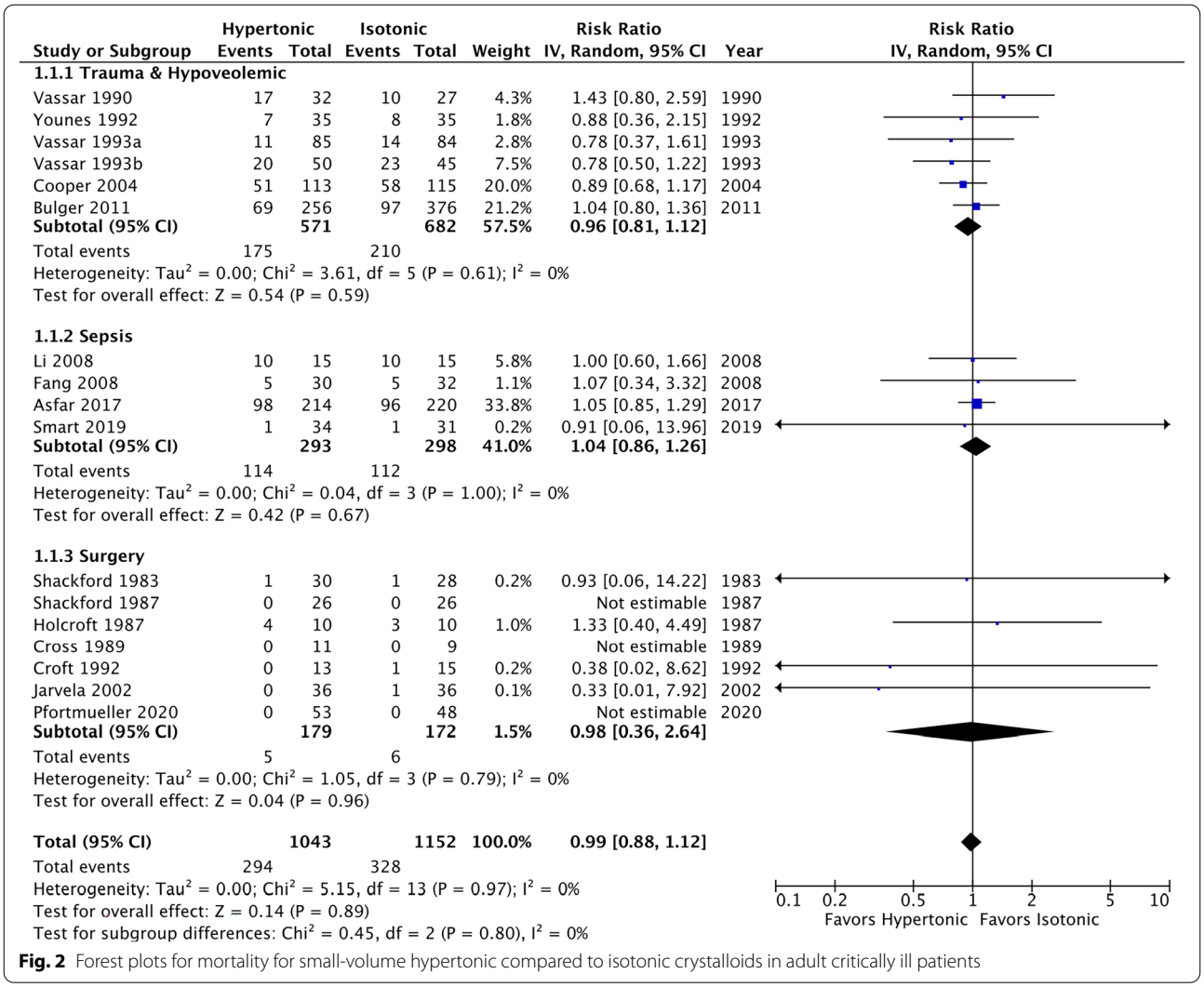


Fig. 2 Forest plots for mortality for small-volume hypertonic compared to isotonic crystalloids in adult critically ill patients

Table 3 Summary of the clinical question and recommendation for small-volume hypertonic or isotonic crystalloids

SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR SMALL-VOLUME HYPERTONIC OR ISOTONIC CRYSTALLOIDS	
Q11 Should small-volume hypertonic or isotonic crystalloids be used for volume expansion in adult critically ill patients?	
R We suggest using isotonic crystalloids rather than small-volume hypertonic fluids for volume expansion in adult critically ill patients.	VERY LOW CERTAINTY OF EVIDENCE

CERTAINTY OF EVIDENCE:
NO EVIDENCE / VERY LOW / LOW / MODERATE / HIGH

Q QUESTION R RECOMMENDATION REMARK

NO RECOMMENDATION CONDITIONAL RECOMMENDATION STRONG RECOMMENDATION
CONDITIONAL RECOMMENDATION AGAINST STRONG RECOMMENDATION AGAINST

Conclusions

In conclusion, these guidelines present 11 evidence-based recommendations (summarized in Tables 1, 2 and 3) regarding the use of albumin, balanced crystalloids and isotonic saline as resuscitation fluid in adult critically ill patients. In addition, research priorities were identified for future studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-024-07369-9.

Author details

[1] Intensive Care Department, King Abdulaziz Medical City, Ministry of National Guard—Health Affairs, King Abdullah International Medical Research Center, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. [2] Divisions of Cardiology and Critical Care, McMaster University, Riyadh, Saudi Arabia. [3] Department of Biomedical Sciences and Public Health, Università Politecnica delle Marche, Ancona, Italy. [4] Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium. [5] Department of Surgery, Dentistry, Gynaecology and Paediatrics, University of Verona, Verona, Italy. [6] Anaesthesia and Intensive Care B Unit, AOUI-University Hospital Integrated Trust of Verona, Verona, Italy. [7] Department of Intensive Care, Erasmus Medical Center, Rotterdam, The Netherlands. [8] Critical Care Program, The George Institute for Global Health and UNSW, Sydney, Australia. [9] Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, Sydney, Australia. [10] Department of Anaesthesiology and Intensive Care Medicine, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway. [11] Department of Critical Care Medicine, Peking Union Medical College Hospital, Beijing, China. [12] Institute of Global Health and Innovation, Division of Medicine, Imperial College, London, UK. [13] IRCCS Humanitas Research Hospital, Department of Anesthesia and Intensive Care Medicine, Rozzano, Italy. [14] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy. [15] Department of Intensive Care, Copenhagen University Hospital—Rigshospitalet, København, Denmark. [16] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [17] Operative Unit of Anesthesia and Intensive Care, S. Martino Hospital, Belluno, Italy. [18] Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, Northern Ireland. [19] Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium. [20] Department of Critical Care Medicine, University of Alberta, Edmonton, Canada. [21] Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates.

Acknowledgements

We thank Jade Shyvers, a patient relative for reviewing the recommendations and providing feedback.

Funding

Panelists received no financial incentives for their participation. In addition, no funding or input from the industry was incorporated into the guideline.

Declarations

Conflicts of interest

YMA: none. EB-C: None. AC: none. DDB: received remuneration from Fresenius, Baxter, Pfizer, Edwards, Philips, and has published and presented on the topic. KD: none. NPJ received unrestricted funding from Octaphrama for investigator driven research on development of fluids for shock treatment that are associated with reduced vascular permeability, and reported publishing on the topic. NH reported that her institute, the George Institute for Global Health, has received research and travel funding from Baxter, Fresenius Karbi, Grifols and CSL. She has several publications related to the topic including Crystalloid vs Hydroxyethyl Starch Trial (CHEST); Fluid TRIPS; Plasma-Lyte vs saline trial (PLUS) and has presented research findings in relation to fluid therapy at national and international critical care conferences. JHL presented on the topic at national and international meetings, one opinion piece in Acta Anaesthesiologica Scandinavia (regarding the use of starches (HES)). DL: none. KM: none. AM received a lecture fee from Baxter. MHM: none. DP: participated in guidelines focused on fluid management in cerebral injury. RMS: none. JLV: none. FGZ received consulting fees from Baxter International and is the PI of the BaSICS trial that received logistic support and fluid donation from Baxter Hospitalar (Brazil). FA: none.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 13 November 2023 Accepted: 20 February 2024
Published: 21 May 2024

References

1. Vincent JL, De Backer D (2013) Circulatory shock. N Engl J Med 369:1726–1734
2. Hammond NE, Taylor C, Finfer S, Machado FR, An Y, Billot L, Bloos F, Bozza F, Cavalcanti AB, Correa M, Du B, Hjortrup PB, Li Y, McIntryre L, Saxena M, Schortgen F, Watts NR, Myburgh J, Fluid-TRIPS and Fluidos Investigators; George Institute for Global Health, The ANZICS Clinical Trials Group, BRICNet, and the REVA research Network (2017) Patterns of intravenous fluid resuscitation use in adult intensive care patients between 2007 and 2014: an international cross-sectional study. PLoS One 12:e0176292
3. Myburgh JA, Mythen MG (2013) Resuscitation fluids. N Engl J Med 369:2462–2463
4. Cecconi M, Kesecioglu J, Azoulay E, European Society of Intensive Care Medicine (2021) Diversity and inclusivity: the way to multidisciplinary intensive care medicine in Europe. Intensive Care Med 47:598–601
5. Alhazzani W, Lewis K, Jaeschke R, Rochwerg B, Moller MH, Evans L, Wilson KC, Patel S, Coopersmith CM, Cecconi M, Guyatt G, Akl EA (2018) Conflicts of interest disclosure forms and management in critical care clinical practice guidelines. Intensive Care Med 44:1691–1698
6. SAFE Study Investigators, Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R (2011) Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 37:86–96
7. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, ALBIOS Study Investigators (2014) Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 370:1412–1421
8. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schunemann HJ (2011) GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 64:395–400
9. Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I (2018) Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev 8:CD000567
10. Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK (2020) Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. Crit Care 24:693
11. Bai Z, Wang L, Wang R, Zou M, Mendez-Sanchez N, Romeiro FG, Cheng G, Qi X (2022) Use of human albumin infusion in cirrhotic patients: a systematic review and meta-analysis of randomized controlled trials. Hepatol Int 16:1468–1483
12. Wan S, Roberts MA, Mount P (2016) Normal saline versus lower-chloride solutions for kidney transplantation. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD010741.pub2
13. Hammond NE, Zampieri FG, Tanna GLD, Garside T, Adigbli D, Cavalcanti AB, Machado FR, Micallef S, Myburgh J, Ramanan M, Rice TW, Semler MW, Young PJ, Venkatesh B, Finfer S, Delaney A, (2022) Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis. NEJM Evidence 1: EVIDoa2100010
14. Zampieri FG, Cavalcanti AB, Di Tanna GL, Damiani LP, Hammond NE, Machado FR, Micallef S, Myburgh J, Ramanan M, Venkatesh B, Rice TW,

Semler MW, Young PJ, Finfer S (2024) Balanced crystalloids versus saline for critically ill patients (BEST-Living): a systematic review and individual patient data meta-analysis. Lancet Respir Med 12(3):237–246
15. Orbegozo D, Vincent JL, Creteur J, Su F (2019) Hypertonic saline in human sepsis: a systematic review of randomized controlled trials. Anesth Analg 128:1175–1184
16. DerSimonian R, Laird N (2015) Meta-analysis in clinical trials revisited. Contemp Clin Trials 45:139–145
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
19. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, Brignardello-Petersen R, Carrasco-Labra A, De Beer H, Hultcrantz M, Kuijpers T, Meerpohl J, Morgan R, Mustafa R, Skoetz N, Sultan S, Wiysonge C, Guyatt G, Schunemann HJ, Group GW (2020) GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 119:126–135
20. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, Group GW (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924–926
21. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH (2011) GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64:401–406
22. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schunemann HJ (2013) GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 66:151–157
23. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schunemann HJ (2013) GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 66:719–725
24. GRADE Handbook. https://gdt.gradepro.org/app/handbook/handbook.html#:~:text=In%20general%2C%20it%20seems%20preferable%20to%20present%20recommendations%20in%20favor%20of%20a%20particular%20management%20approach%20rather%20than%20against%20an%20alternative. Accessed March 24–2024
25. Michel CC, Woodcock TE, Curry FE (2020) Understanding and extending the Starling principle. Acta Anaesthesiol Scand 64:1032–1037
26. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, SAFE Study Investigators (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256
27. Runken MC, Caraceni P, Fernandez J, Zipprich A, Carlton R, Bunke M (2019) The cost-effectiveness of albumin in the treatment of decompensated cirrhosis in Germany, Italy, and Spain. Health Econ Rev 9:22
28. Taylor C, Yang L, Finfer S, Machado FR, YouZhong A, Billot L, Bloos F, Bozza F, Cavalcanti AB, Correa M, Du B, Hjortrup PB, McIntyre L, Saxena M, Schortgen F, Watts NR, Myburgh J, Thompson K, Hammond NE, Fluid-TRIPS and Fluidos Investigators, The George Institute for Global Health, The ANZICS Clinical Trials Group, BRICNet, and the REVA Research Network (2021) An international comparison of the cost of fluid resuscitation therapies. Aust Crit Care 34:23–32
29. Farrugia A, Bansal M, Balboni S, Kimber MC, Martin GS, Cassar J (2014) Choice of fluids in severe septic patients—a cost-effectiveness analysis informed by recent clinical trials. Rev Recent Clin Trials 9:21–30
30. Guidet B, Mosqueda GJ, Priol G, Aegerter P (2007) The COASST study: cost-effectiveness of albumin in severe sepsis and septic shock. J Crit Care 22:197–203
31. Tigabu B, Davari M, Kebriaeezadeh A, Mojtahedzadeh M, Sadeghi K, Jahangard-Rafsanjani Z (2019) Is albumin-based resuscitation in severe sepsis and septic shock justifiable? An evidence from a cost-effectiveness evaluation. Ethiop J Health Sci 29:869–876
32. Tigabu BM, Davari M, Kebriaeezadeh A, Mojtahedzadeh M, Sadeghi K, Najmeddin F, Jahangard-Rafsanjani Z (2019) A cost-effectiveness analysis of albumin in septic shock: a patient-level data analysis. Clin Ther 41(2297–2307):e2292
33. Vincent JL, Wilkes MM, Navickis RJ (2003) Safety of human albumin–serious adverse events reported worldwide in 1998–2000. Br J Anaesth 91:625–630
34. von Hoegen I, Waller C (2001) Safety of human albumin based on spontaneously reported serious adverse events. Crit Care Med 29:994–996
35. Zampieri FG, Bagshaw SM, Semler MW (2023) Fluid therapy for critically Ill adults with sepsis: a review. JAMA 329:1967–1980
36. Hahn RG (2020) Understanding volume kinetics. Acta Anaesthesiol Scand 64:570–578
37. Kremer H, Baron-Menguy C, Tesse A, Gallois Y, Mercat A, Henrion D, Andriantsitohaina R, Asfar P, Meziani F (2011) Human serum albumin improves endothelial dysfunction and survival during experimental endotoxemia: concentration-dependent properties. Crit Care Med 39:1414–1422
38. Hogue B, Chagnon F, Lesur O (2012) Resuscitation fluids and endotoxin-induced myocardial dysfunction: is selection a load-independent differential issue? Shock 38:307–313
39. Vincent JL, De Backer D, Wiedermann CJ (2016) Fluid management in sepsis: the potential beneficial effects of albumin. J Crit Care 35:161–167
40. Semler MW, Rice TW (2016) Sepsis resuscitation: fluid choice and dose. Clin Chest Med 37:241–250
41. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, Preiser JC, Outin H, Troche G, Charpentier C, Trouillet JL, Kimmoun A, Forceville X, Darmon M, Lesur O, Reignier J, Abroug F, Berger P, Clec'h C, Cousson J, Thibault L, Chevret S, Investigators C (2013) Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA 310:1809–1817
42. SAFE Study Investigators, Finfer S, Bellomo R, McEvoy S, Lo SK, Myburgh J, Neal B, Norton R (2006) Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ 333:1044
43. Malbrain M, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, Teboul JL, Rice TW, Mythen M, Monnet X (2018) Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care 8:66
44. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE Investigators; ESICM Trials Group (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315:788–800
45. Pisani L, Algera AG, Neto AS, Azevedo L, Pham T, Paulus F, de Abreu MG, Pelosi P, Dondorp AM, Bellani G, Laffey JG, Schultz MJ, ERICC study investigators; LUNG SAFE study investigators; PRoVENT study investigators; PRoVENT-iMiC study investigators (2022) Geoeconomic variations in epidemiology, ventilation management, and outcomes in invasively ventilated intensive care unit patients without acute respiratory distress syndrome: a pooled analysis of four observational studies. Lancet Glob Health 10:e227–e235
46. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS (2019) Acute respiratory distress syndrome. Nat Rev Dis Primers 5:18
47. Mendes RS, Pelosi P, Schultz MJ, Rocco PRM, Silva PL (2020) Fluids in ARDS: more pros than cons. Intensive Care Med Exp 8:32
48. Uhlig C, Silva PL, Deckert S, Schmitt J, de Abreu MG (2014) Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care 18:R10
49. Metildi LA, Shackford SR, Virgilio RW, Peters RM (1984) Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. Surg Gynecol Obstet 158:207–212
50. van der Heijden M, Verheij J, van Nieuw Amerongen GP, Groeneveld AB (2009) Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. Crit Care Med 37:1275–1281
51. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J (2017) Guidelines

for the management of severe traumatic brain injury, fourth edition. Neurosurgery 80:6–15
52. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health; Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S (2007) Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 357:874–884
53. Cooper DJ, Myburgh J, Heritier S, Finfer S, Bellomo R, Billot L, Murray L, Vallance S, SAFE-TBI Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group (2013) Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? J Neurotrauma 30:512–518
54. Iguchi N, Kosaka J, Bertolini J, May CN, Lankadeva YR, Bellomo R (2018) Differential effects of isotonic and hypotonic 4% albumin solution on intracranial pressure and renal perfusion and function. Crit Care Resusc 20:48–53
55. Wiedermann CJ (2022) Use of hyperoncotic human albumin solution in severe traumatic brain injury revisited—a narrative review and meta-analysis. J Clin Med 11:2662
56. Kozek-Langenecker SA (2015) Fluids and coagulation. Curr Opin Crit Care 21:285–291
57. Rasmussen KC, Secher NH, Pedersen T (2016) Effect of perioperative crystalloid or colloid fluid therapy on hemorrhage, coagulation competence, and outcome: a systematic review and stratified meta-analysis. Medicine (Baltimore) 95:e4498
58. Hussmann B, Lefering R, Waydhas C, Touma A, Kauther MD, Ruchholtz S, Lendemans S, Trauma Registry of the German Society for Trauma Surgery (2013) Does increased prehospital replacement volume lead to a poor clinical course and an increased mortality? A matched-pair analysis of 1896 patients of the Trauma Registry of the German Society for Trauma Surgery who were managed by an emergency doctor at the accident site. Injury 44:611–617
59. Durand F, Kellum JA, Nadim MK (2023) Fluid resuscitation in patients with cirrhosis and sepsis: a multidisciplinary perspective. J Hepatol 79:240–246
60. Valerio C, Theocharidou E, Davenport A, Agarwal B (2016) Human albumin solution for patients with cirrhosis and acute on chronic liver failure: beyond simple volume expansion. World J Hepatol 8:345–354
61. Best LM, Freeman SC, Sutton AJ, Cooper NJ, Tng EL, Csenar M, Hawkins N, Pavlov CS, Davidson BR, Thorburn D, Cowlin M, Milne EJ, Tsochatzis E, Gurusamy KS (2019) Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis. Cochrane Database Syst Rev 9:CD013103
62. Benmassaoud A, Freeman SC, Roccarina D, Plaz Torres MC, Sutton AJ, Cooper NJ, Iogna Prat L, Cowlin M, Milne EJ, Hawkins N, Davidson BR, Pavlov CS, Thorburn D, Tsochatzis E, Gurusamy KS (2020) Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis. Cochrane Database Syst Rev 1:CD013123
63. Simonetti RG, Perricone G, Nikolova D, Bjelakovic G, Gluud C (2019) Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis. Cochrane Database Syst Rev 6:CD004039
64. Leao GS, John Neto G, Jotz RF, Mattos AA, Mattos AZ (2019) Albumin for cirrhotic patients with extraperitoneal infections: a meta-analysis. J Gastroenterol Hepatol 34:2071–2076
65. Bombassaro IZ, Tovo CV, de Mattos AZ, Ahlert M, Chiesa T, de Mattos AA (2021) Albumin in the management of hepatic encephalopathy: a systematic review and meta-analysis. Ann Hepatol 26:100541
66. Teh KB, Loo JH, Tam YC, Wong YJ (2021) Efficacy and safety of albumin infusion for overt hepatic encephalopathy: a systematic review and meta-analysis. Dig Liver Dis 53:817–823
67. Ashour AA, Atta MA, Sadek KW, Obaid KR, Ashour MA, Ashour A, Danjuma MI, Doi SA, ElZouki AN (2021) Albumin administration in patients with decompensated liver cirrhosis: a meta-analytic update. Eur J Gastroenterol Hepatol 33:479–486
68. Xu T, Liu W, Huang R (2023) Can albumin reduce the mortality of patients with cirrhosis and ascites? A meta-analysis of randomized controlled trials. Eur J Gastroenterol Hepatol 35:80–88
69. Zaccherini G, Tufoni M, Bernardi M (2020) Albumin administration is efficacious in the management of patients with cirrhosis: a systematic review of the literature. Hepat Med 12:153–172
70. Simon-Talero M, Garcia-Martinez R, Torrens M, Augustin S, Gomez S, Pereira G, Guevara M, Gines P, Soriano G, Roman E, Sanchez-Delgado J, Ferrer R, Nieto JC, Sunye P, Fuentes I, Esteban R, Cordoba J (2013) Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. J Hepatol 59:1184–1192
71. Philips CA, Maiwall R, Sharma MK, Jindal A, Choudhury AK, Kumar G, Bhardwaj A, Mitra LG, Agarwal PM, Sarin SK (2021) Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. Hepatol Int 15:983–994
72. Maiwall R, Kumar A, Pasupuleti SSR, Hidam AK, Tevethia H, Kumar G, Sahney A, Mitra LG, Sarin SK (2022) A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. J Hepatol 77:670–682
73. Freitas FGR, Hammond N, Li Y, Azevedo LCP, Cavalcanti AB, Taniguchi L, Gobatto A, Japiassu AM, Bafi AT, Mazza BF, Noritomi DT, Dal-Pizzol F, Bozza F, Salluh JIF, Westphal GA, Soares M, Assuncao MSC, Lisboa T, Lobo SMA, Barbosa AR, Ventura AF, Souza AF, Silva AF, Toledo A, Reis A, Cembranel A, Rea Neto A, Gut AL, Justo APP, Santos AP, Albuquerque ACD, Scazufka A, Rodrigues AB, Fernandino BB, Silva BG, Vidal BS, Pinheiro BV, Pinto BVC, Feijo CAR, Abreu Filho C, Bosso C, Moreira CEN, Ramos CHF, Tavares C, Arantes C, Grion C, Mendes CL, Kmohan C, Piras C, Castro CPP, Lins C, Beraldo D, Fontes D, Boni D, Castiglioni D, Paisani DM, Pedroso DFF, Mattos ER, Brito Sobrinho E, Troncoso EMV, Rodrigues Filho EM, Nogueira EEF, Ferreira EL, Pacheco ES, Jodar E, Ferreira ELA, Araujo FF, Trevisol FS, Amorim FF, Giannini FP, Santos FPM, Buarque F, Lima FG, Costa F, Sad F, Aranha FG, Ganem F, Callil F, Costa Filho FF, Dall Arto FTC, Moreno G, Friedman G, Moralez GM, Silva GAD, Costa G, Cavalcanti GS, Cavalcanti GS, Betonico GN, Betonico GN, Reis H, Araujo HBN, Hortiz Junior HA, Guimaraes HP, Urbano H, Maia I, Santiago Filho IL, Farhat Junior J, Alvarez JR, Passos JT, Paranhos J, Marques JA, Moreira Filho JG, Andrade JN, Sobrinho JOC, Bezerra JTP, Alves JA, Ferreira J, Gomes J, Sato KM, Gerent K, Teixeira KMC, Conde KAP, Martins LF, Figueiredo L, Rezegue L, Tcherniacovsk L, Ferraz LO, Cavalcante L, Rabelo L, Miilher L, Garcia L, Tannous L, Hajjar LA, Paciencia LEM, Cruz Neto LMD, Bley MV, Sousa MF, Puga ML, Romano MLP, Nobrega M, Arbex M, Rodrigues ML, Guerreiro MO, Rocha M, Alves MAP, Alves MAP, Rosa MD, Dias MD, Martins M, Oliveira M, Moretti MMS, Matsui M, Messender O, Santarem OLA, Silveira P, Vassallo PF, Antoniazzi P, Gottardo PC, Correia P, Ferreira P, Torres P, Silva P, Foernges R, Gomes R, Moraes R, Nonato Filho R, Borba RL, Gomes RV, Cordioli R, Lima R, Lopez RP, Gargioni RRO, Rosenblat R, Souza RM, Almeida R, Narciso RC, Marco R, Waltrick R, Biondi R, Figueiredo R, Dutra RS, Batista R, Felipe R, Franco R, Houly S, Faria SS, Pinto SF, Luzzi S, Sant'ana S, Fernandes SS, Yamada S, Zajac S, Vaz SM, Bezerra SAB, Farhat TBT, Santos TM, Smith T, Silva UVA, Damasceno VB, Nobre V, Dantas VCS, Irineu VM, Bogado V, Nedel W, Campos Filho W, Dantas W, Viana W, Oliveira Filho W, Delgadinho WM, Finfer S, Machado FR (2021) Resuscitation fluid practices in Brazilian intensive care units: a secondary analysis of Fluid-TRIPS. Rev Bras Ter Intensiva 33:206–218
74. Finfer S, Myburgh J, Bellomo R (2018) Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol 14:541–557
75. Soussi S, Ferry A, Chaussard M, Legrand M (2017) Chloride toxicity in critically ill patients: what's the evidence? Anaesth Crit Care Pain Med 36:125–130
76. Hammond DA, Lam SW, Rech MA, Smith MN, Westrick J, Trivedi AP, Balk RA (2020) Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. Ann Pharmacother 54:5–13
77. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J, Investigators ST (2010) Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 14:R185
78. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M (2012) Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 308:1566–1572
79. Brown RM, Wang L, Coston TD, Krishnan NI, Casey JD, Wanderer JP, Ehrenfeld JM, Byrne DW, Stollings JL, Siew ED, Bernard GR, Self WH, Rice TW, Semler MW (2019) Balanced crystalloids versus saline in sepsis. a

secondary analysis of the SMART clinical trial. Am J Respir Crit Care Med 200:1487–1495
80. Raghunathan K, Shaw A, Nathanson B, Sturmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK (2014) Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 42:1585–1591
81. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R, Investigators S, ANZICS CTG (2015) Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA 314:1701–1710
82. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, Wang L, Byrne DW, Shaw AD, Bernard GR, Rice TW, SI, the Pragmatic Critical Care Research G, Investigators S (2017) Balanced crystalloids versus saline in the intensive care unit the SALT randomized trial. Am J Respir Crit Care Med 195:1362–1372
83. Semler MW, Self WH, Rice TW (2018) Balanced crystalloids versus saline in critically ill adults. N Engl J Med 378:1951
84. Finfer S, Micallef S, Hammond N, Navarra L, Bellomo R, Billot L, Delaney A, Gallagher M, Gattas D, Li Q, Mackle D, Mysore J, Saxena M, Taylor C, Young P, Myburgh J, PLUS Study Investigators and the Australian New Zealand Intensive Care Society Clinical Trials Group (2022) Balanced multielectrolyte solution versus saline in critically ill adults. N Engl J Med 386:815–826
85. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, Lovato WJ, Amendola CP, Serpa-Neto A, Paranhos JLR, Guedes MAV, Lucio EA, Oliveira-Junior LC, Lisboa TC, Lacerda FH, Maia IS, Grion CMC, Assuncao MSC, Manoel ALO, Silva-Junior JM, Duarte P, Soares RM, Miranda TA, de Lima LM, Gurgel RM, Paisani DM, Correa TD, Azevedo LCP, Kellum JA, Damiani LP, Brandao da Silva N, Cavalcanti AB, BaSICS investigators and the BRICNet members (2021) Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: the BaSICS randomized clinical trial. JAMA 326:1–12
86. Ramming S, Shackford SR, Zhuang J, Schmoker JD (1994) The relationship of fluid balance and sodium administration to cerebral edema formation and intracranial pressure in a porcine model of brain injury. J Trauma 37:705–713
87. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ (1999) The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 88:999–1003
88. Rowell SE, Fair KA, Barbosa RR, Watters JM, Bulger EM, Holcomb JB, Cohen MJ, Rahbar MH, Fox EE, Schreiber MA (2016) The impact of pre-hospital administration of lactated ringer's solution versus normal saline in patients with traumatic brain injury. J Neurotrauma 33:1054–1059
89. Lombardo S, Smith MC, Semler MW, Wang L, Dear ML, Lindsell CJ, Freundlich RE, Guillamondegui OD, Self WH, Rice TW, Isotonic S, Major Adverse Renal Events Trial I, Vanderbilt Learning Healthcare System Platform I (2022) Balanced crystalloid versus saline in adults with traumatic brain injury: secondary analysis of a clinical trial. J Neurotrauma 39:1159–1167
90. Papasotiriou M, Mpratsiakou A, Georgopoulou G, Ntrinias T, Balta L, Pavlakou P, Goumenos DS, Papachristou E (2023) Normal saline versus balanced crystalloids in patients with prerenal acute kidney injury and pre-existing chronic kidney disease. Rom J Intern Med 61:98–105
91. Jahangir A, Sahra S, Niazi MRK, Siddiqui FS, Anwar MY, Jahangir A, El-Charabaty EJ (2021) Comparison of normal saline solution with low-chloride solutions in renal transplants: a meta-analysis. Kidney Res Clin Pract 40:484–495
92. Wagener G, Bezinover D, Wang C, Kroepfl E, Diaz G, Giordano C, West J, Kindscher JD, Moguilevitch M, Nicolau-Raducu R, Planinsic RM, Rosenfeld DM, Lindberg S, Schumann R, Pivalizza EG (2021) Fluid management during kidney transplantation: a consensus statement of the committee on transplant anesthesia of the American Society of Anesthesiologists. Transplantation 105:1677–1684
93. Collins MG, Fahim MA, Pascoe EM, Hawley CM, Johnson DW, Varghese J, Hickey LE, Clayton PA, Dansie KB, McConnochie RC, Vergara LA, Kiriwandeniya C, Reidlinger D, Mount PF, Weinberg L, McArthur CJ, Coates PT, Endre ZH, Goodman D, Howard K, Howell M, Jamboti JS, Kanellis J, Laurence JM, Lim WH, McTaggart SJ, O'Connell PJ, Pilmore HL, Wong G, Chadban SJ, BEST-Fluids Investigators; Australasian Kidney Trials Network (2023) Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial. Lancet 402:105–117
94. Drobin D, Hahn RG (2002) Kinetics of isotonic and hypertonic plasma volume expanders. Anesthesiology 96:1371–1380
95. Wiegers EJA, Lingsma HF, Huijben JA, Cooper DJ, Citerio G, Frisvold S, Helbok R, Maas AIR, Menon DK, Moore EM, Stocchetti N, Dippel DW, Steyerberg EW, van der Jagt M, CENTER-TBI; OzENTER-TBI Collaboration Groups (2021) Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study. Lancet Neurol 20:627–638
96. Oliveira RP, Velasco I, Soriano FG, Friedman G (2002) Clinical review: hypertonic saline resuscitation in sepsis. Crit Care 6:418–423
97. Pascual JL, Khwaja KA, Ferri LE, Giannias B, Evans DC, Razek T, Michel RP, Christou NV (2003) Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. J Trauma 54:121–130
98. Dubick MA, Atkins JL (2003) Small-volume fluid resuscitation for the far-forward combat environment: current concepts. J Trauma 54:S43-45
99. Smith JE, Hall MJ (2004) Hypertonic saline. J R Army Med Corps 150:239–243
100. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, Investigators HTSS (2004) Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA 291:1350–1357
101. Orbegozo Cortes D, Rayo Bonor A, Vincent JL (2014) Isotonic crystalloid solutions: a structured review of the literature. Br J Anaesth 112:968–981
102. Roquilly A, Moyer JD, Huet O, Lasocki S, Cohen B, Dahyot-Fizelier C, Chalard K, Seguin P, Jeantrelle C, Vermeersch V, Gaillard T, Cinotti R, Demeure Dit Latte D, Mahe PJ, Vourc'h M, Martin FP, Chopin A, Lerebourg C, Flet L, Chiffoleau A, Feuillet F, Asehnoune K (2021) Effect of continuous infusion of hypertonic saline vs standard care on 6-month neurological outcomes in patients with traumatic brain injury: the COBI randomized clinical trial. JAMA 325:2056–2066
103. Li B, Zhao H, Zhang J, Yan Q, Li T, Liu L (2020) Resuscitation fluids in septic shock: a network meta-analysis of randomized controlled trials. Shock 53:679–685
104. Bunn F, Roberts I, Tasker R, Akpa E (2004) Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2004:CD002045
105. Safiejko K, Smereka J, Pruc M, Ladny JR, Jaguszewski MJ, Filipiak KJ, Yakubtsevich R, Szarpak L (2022) Efficacy and safety of hypertonic saline solutions fluid resuscitation on hypovolemic shock: a systematic review and meta-analysis of randomized controlled trials. Cardiol J 29:966–977
106. Pfortmueller CA, Schefold JC (2017) Hypertonic saline in critical illness—a systematic review. J Crit Care 42:168–177
107. Wu MC, Liao TY, Lee EM, Chen YS, Hsu WT, Lee MG, Tsou PY, Chen SC, Lee CC (2017) Administration of hypertonic solutions for hemorrhagic shock: a systematic review and meta-analysis of clinical trials. Anesth Analg 125:1549–1557
108. Shrum B, Church B, McArthur E, Burns KE, Znajda T, McAlister V (2016) Hypertonic salt solution for peri-operative fluid management. Cochrane Database Syst Rev 2016:CD005576